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Roxithromycin-Associated Acute Thrombocytopenia

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABEF Marco Rossi
B Matteo Capecchi
E Pietro E. Lazzerini

Department of Medical Sciences, Surgery, and Neurosciences, University of Siena, Siena, Italy

Corresponding Author: Marco Rossi, e-mail: marco.rossi@unisi.it
Conflict of interest: None declared

Patient: Female, 78-year-old
Final Diagnosis: Acute autoimmune thrombocytopenia
Symptoms: Petechial lesions of the palate • two hematomas of the tongue and purpuric macules with central crust in the abdomen and in the left lower limb
Medication: —
Clinical Procedure: —
Specialty: Hematology • Pharmacology and Pharmacy

Objective: Unusual or unexpected effect of treatment

Background: Recently, some case reports have been published on the macrolide antimicrobials azithromycin and clarithromycin as the cause of thrombocytopenia. The publicly accessible databases of the European Medicine Agency and the WHO drug monitoring program contain dozens of reports of roxithromycin-associated thrombocytopenia.

Case Report: We described the case of a 78-year-old woman presenting to our unit with petechial lesions of the palate, 2 hematomas of the tongue, and purpuric macules in the abdomen and in the left lower limb 4 days after a course of roxithromycin. She presented to the Emergency Department with 3 out-of-range blood test results: neutrophils (11 960/mL; range: 1500-7000/mL), platelet count (3000/mL; range: 150 000-400 000/mL), and lactate dehydrogenase (379 IU/L; range: 135-225 IU/L). Thrombocytopenia occurred in the absence of aggregates and observed nucleolated lymphocytes. Lymphoproliferative pathologies and thrombotic microangiopathy were excluded by the hematologist. To rule out neoplastic lesions, an abdominal ultrasound examination was made. Antibody screening was performed for antinuclear antibodies, extractable nuclear antigen, antineutrophil cytoplasmic antibodies (all negative), and for Parvovirus B-19 (IgM negative, IgG positive), as well as HHV-6 and HHV-8 (both negative), to exclude an autoimmune or viral etiology. She recovered after intravenous methylprednisolone 60 mg/day and intravenous-immunoglobulin therapy 400 mg/kg/day. After 9 days, the patient was discharged with resolution of skin and buccal lesions. Her platelet count was 515 000/mL.

Conclusions: To the best of our knowledge, this is the first case of roxithromycin-associated acute autoimmune thrombocytopenia reported in the medical literature. We suggest that clinicians should consider this drug to be among the possible causes of drug-induced thrombocytopenia.

Keywords: Drug-Related Side Effects and Adverse Reactions • Roxithromycin • Thrombocytopenia

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/932039

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Background

The first case of quinine-induced thrombocytopenia was identified 156 years ago [1]. Recently, some case reports of macrolide antibiotics, namely azithromycin [2,3] and clarithromycin [4], as the cause of autoimmune thrombocytopenia have been published in the medical literature. Autoimmune thrombocytopenia can be caused by drugs, but it can have many other etiopathogeneses, thus the diagnosis of drug-induced thrombocytopenia (DIT) can easily be overlooked, especially in hospitalized patients. Although DIT is rare, it can have severe consequences; therefore, it is important that clinicians perform a differential diagnosis of this condition, keeping in mind that hundreds of drugs can cause it. We herein report a case of roxithromycin-associated acute thrombocytopenia.

Case Report

A 78-year-old woman was admitted to our internal medicine unit after Emergency Department (ED) and acute ward stay in our institution. She had been sent from another ED for otolaryngological and dermatological evaluation in suspected Adverse Drug Reaction (ADR), as she was prescribed roxithromycin, dose unknown, for bronchitis 4 days before the onset of the symptoms. She was also on long-term treatment with paroxetine 10 mg/day for anxious depressive syndrome. In our ED she presented with 3 out-of-range blood test results: neutrophils (11 960/mL; range: 1500-7000/mL), platelet count (3000/mL; range: 150 000-400 000/mL), and lactate dehydrogenase (379 IU/l; range: 135-225 IU/l). The hematologist excluded the hypothesis of thrombotic microangiopathy, given the absence of anemia and schistocytes in the peripheral smear, confirmed the presence of severe thrombocytopenia in the absence of aggregates and observed nucleolated lymphocytes for which ad hoc examination was performed to exclude the presence of lymphoproliferative pathology underlying the immune-mediated thrombocytopenia. Intravenous therapy with methylprednisolone 60 mg/day and intravenous-immunoglobulin (IVIG) 400 mg/kg/day was started. Dermatological assessment reported non-bleeding vascular exophytic lesions of the dorsal portion and sides of the tongue and purpuric macules with central crust in the abdomen and in the left lower limb. Otolaryngological evaluation in fibroscopy showed a strongly inflamed larynx with hemorrhagic areas and erythematous vocal cords. On admission to our unit, the patient was conscious, oriented, cooperating, and without side deficit. On physical examination, the skin and the visible mucous membranes were hydrated, with petechial lesions of the palate and 2 hematomas of the tongue (**Figure 1**).

The corticosteroid and IVIG therapy started by the hematologist was continued. The immunotype was within the limits,

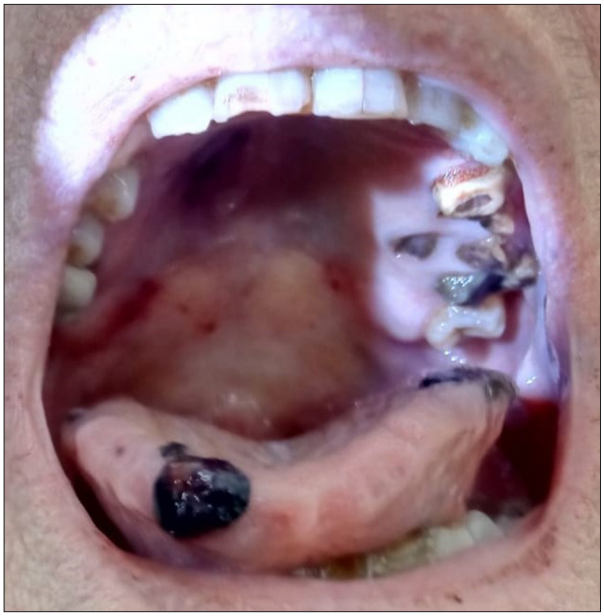

Figure 1. Petechial lesions of the palate and hematomas of the tongue on admission to our unit.

while the markers for hepatotropic viruses showed previous infections for viruses HV-A and HV-B. To exclude neoplastic lesions, we made an abdominal ultrasound examination, which reported a liver of regular volume with a slight steatosis without evident focal lesions, non-lithic gallbladder, non-dilated biliary tract, no echo-detectable alterations of pancreas, spleen, and kidneys, no signs of bilaterally obstructive uropathy, normal caliber of abdominal aorta, poorly assessable empty bladder, and no peritoneal fluid. The otolaryngological re-evaluation reported the disappearance of the previously observed lesions of the oral cavity and the persistence of inflammation of the vocal cords and hemorrhagic areas in the posterior third of the same, hyperemic nasopharynx and some vascular ectasia of the base of the tongue. Antibody screening was performed for antinuclear antibodies, extractable nuclear antigen, antineutrophil cytoplasmic antibodies (all negative) and for Parvovirus B-19 (IgM negative, IgG positive), HHV-6 and HHV-8 (both negative) to exclude a possible autoimmune or viral etiology. Furthermore, a protein electrophoresis was executed, which showed hypoalbuminemia, hypergammaglobulinemia, normal protein level (7 g/dL; range: 6.0-8.0 g/dl), increased kappa and lambda chains (622 mg/dl; range: 170-370 mg/dl; and 313 mg/dL: range: 90-210 mg/dL, respectively), and normal immunofixation. Seven days after roxithromycin withdrawal and 4 days after corticosteroid and IVIG therapy initiation, the platelet level was normal (245 000/mL) and there was a reduction in hematomas. After 9 days the patient was discharged in good clinical condition with resolution of skin and buccal lesions. Her platelet count was 515 000/mL.

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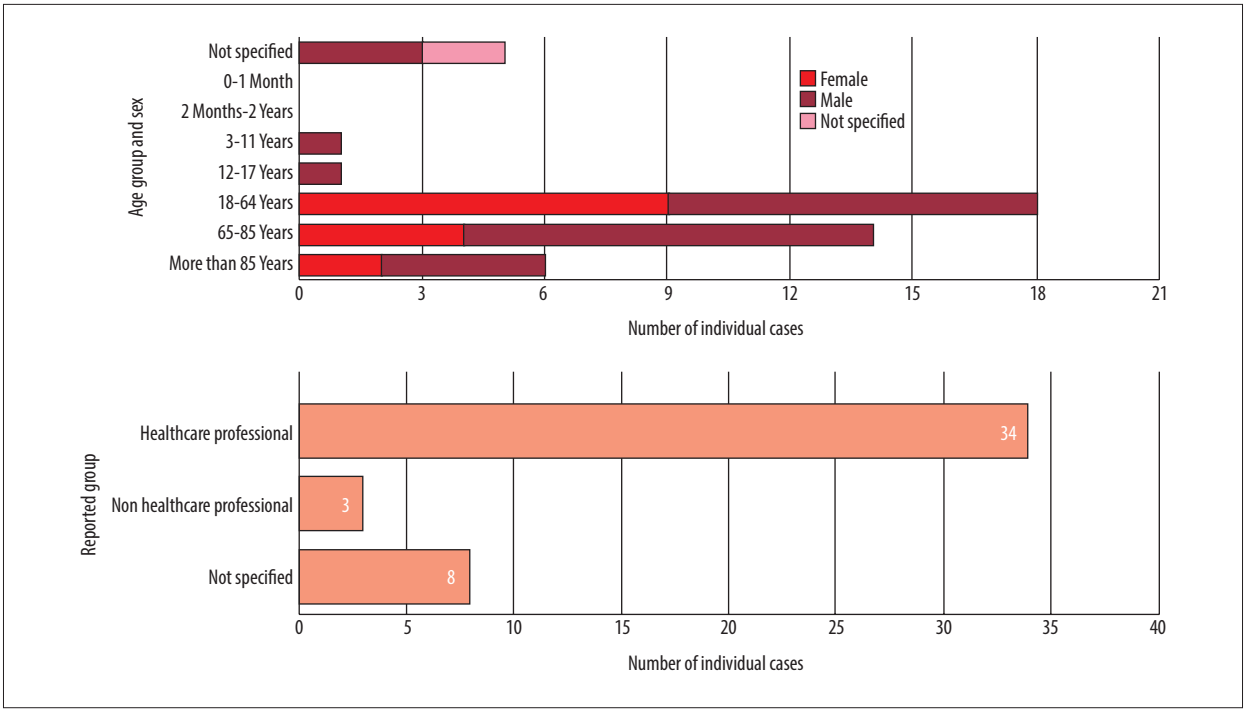

Figure 2. Reports of 45 individual cases of thrombocytopenia associated with roxithromycin present in the database Eudravigilance, stratified for age, sex, and reporter, as downloaded from www.adrreports.eu on 02/09/2021.

Discussion

To date, 4 cases of thrombocytopenia after the exposure to clarithromycin, 2 of them presenting with cutaneous petechiae, [4-7] and 2 cases of azithromycin-induced thrombocytopenia have been reported in the literature. DIT can result from bone marrow toxicity or immune-mediated destruction of platelets. The diagnosis of autoimmune DIT is generally based on therapy with a suspected drug that precedes thrombocytopenia by a sufficient time to development of antibodies, the exclusion of all other reasonable causes of thrombocytopenia, recovery that occurs after the withdrawal of the culprit drug, and the eventual rechallenge, if ethical, that leads to recurrent thrombocytopenia. However, these criteria are rarely met, as underlying clinical circumstances are often complex and introduction and withdrawal of multiple drugs within a short time frame is common. Moreover, testing for drug-dependent antibodies is rarely possible. DIT is a rare ADR: on the basis of several epidemiologic studies in the United States and Europe, the estimated minimum incidence of DIT is 10 cases/million patients/year [8], but the number may be higher in selected populations, such as hospitalized patients and elderly people. Diverse etiopathogenetic mechanisms have been postulated to cause DIT, including immune complexes (heparin), induction of autoantibody (gold salts), antidrug-specific antibodies (abciximab), drugs that induce conformational changes in platelet antigens that are recognized by antibody (fiban drugs), drug-induced antibodies that bind to platelet membranes in the presence of a soluble agent (quinine), and hapten-dependent antibodies (beta-lactam antibiotics) [9]. Initial treatment for immune-mediated DIT is to discontinue the medication, causing symptoms to be improved within 2 days and platelet count increases to normal range within 1 week [8]. In our case, platelets count became normal 7 days after roxithromycin withdrawal and 4 days after receiving corticosteroids and IVIG. We can classify our case a probable case of DIT with level of evidence 2 (criteria 1-3) [10,11], as therapy with roxithromycin occurred before thrombocytopenia (criterion 1), other etiologies were excluded (criterion 3), and platelet count quickly recovered after discontinuing roxithromycin (criterion 2), which was the only drug used before thrombocytopenia. We also applied the Naranjo ADR probability scale [12], a widely used score developed to standardize assessment of causality for ADR, categorizing our case as "probable" (score 6, "probable" range: 5-8). In the database of European Medicine Agency "Eudravigilance", which retains suspected ADRs from 2005, we retrieved 45 cases coded with Medical Dictionary for Regulatory Activities (MedDRA) as thrombocytopenia, associated to the use of roxithromycin [13]. These cases, stratified for age, sex, and reporter, are shown in **Figure 2**. In a much longer period, as the WHO drug monitoring program began in 1968, 70 cases of thrombocytopenia related to the use of roxithromycin have been entered in the database VigiBase® [14]. Our case is registered in both databases with WorldWideID code IT-MINSAL02-606920; thus, 44 and 69 are possible additional cases, respectively.

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Conclusions

To the best of our knowledge, despite several notifications to regulatory agencies, this is the first case of roxithromycin-associated acute autoimmune thrombocytopenia reported in the medical literature. We suggest that clinicians should consider this drug to be among the possible causes of DIT.

Conflicts of Interest

None.

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